HHS Public Access

Author manuscript

J Affect Disord. Author manuscript; available in PMC 2021 November 01.

Published in final edited form as:

J Affect Disord. 2020 November 01; 276: 453–460. doi:10.1016/j.jad.2020.07.025.

Treating Major Depression and Comorbid Disorders with Transcranial Magnetic Stimulation

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Abstract

Background: Major Depressive Disorder (MDD) is a global disorder that negatively affects mood and quality of life. Antidepressant medication and psychotherapy are the most commonly prescribed treatments, but prior research has called their clinical efficacy into question. These treatments may be less effective when the patient has a diagnosed comorbid disorder.

Method: A systematic review of the literature was conducted to investigate whether an alternative method of treatment, Transcranial Magnetic Stimulation (TMS), is effective for MDD with a diagnosed comorbidity. 110 articles were identified, of which 8 were included in the current review.

Results: Response and remission rates vary. A range of 39.5-70% of participants experienced an antidepressant response to treatment, and 16.6-76.9% of patients achieved remission from MDD. A range of 48.6-84.6% of participants responded to treatment of their comorbid disorder, and 50-84.6% achieved remission of comorbid symptoms.

Limitations: Limitations of the current review include small sample sizes, limited statistical power, homogenous samples, and a lack of sham or placebo-controlled studies.

Conclusion: Preliminary results support that TMS is effective at treating symptoms of MDD and a comorbid disorder. Additional studies are needed to confirm these results.

Keywords

major depressive disorder; transcranial magnetic stimulation; comorbidity

Major depressive disorder (MDD) is a mood disorder characterized by depressed mood or loss of interest or pleasure (American Psychological Association, 2013). Additional possible symptoms include fluctuations in body mass, appetite, and sleep; psychomotor agitation;

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Contributions

Lauren Thompson was responsible for establishing review criteria and searching for articles, analyzing articles, and writing the systematic review. Dr. Lisa Weyandt read the initial draft and provided feedback (included in the Acknowledgments).

Declarations of Interest

The author has no conflicts of interest to declare.

feelings of worthlessness; indecisiveness or difficulty concentrating; and suicidal ideation (American Psychological Association, 2013). MDD is among one of the most prevalent mental health disorders globally, with lifetime prevalence rates ranging from 2.9-21.0% and an average of 10.6% based on data from the 29 countries included in the World Health Organization (WHO) World Mental Health (WMH) Surveys Initiative (Bromet et al., 2018). According to WMH data, lifetime prevalence rates within the United States average 16.9%, with women showing higher prevalence than men (20.2% vs. 13.2%) (Bromet et al., 2018).

Depression typically exerts significant negative effects on the lives of those diagnosed. As of 2017, depressive disorders are the third leading cause of years lived with disability (YLDs) for women worldwide, and the fifth leading cause of YLDs for men (James et al., 2018). A 2014 study of adult inpatients with MDD found that pain and depression had a direct negative effect on daily functioning and quality of life (QOL) (Lin et al., 2014), while a recent study of adult outpatients with MDD or bipolar disorder (BP) found that depression severity was negatively correlated to QOL in both disorders (Gao et al., 2019). Major depression has also been linked to impaired executive functioning (Ahern and Semkovska, 2017; Snyder, 2013). Executive functions are a set of top-down cognitive processes that control planning and goal-oriented behavior and are necessary for daily life tasks (Diamond, 2013; Miyake et al., 2000). Depression is also comorbid with a number of other disorders; data from the WHO WMH Surveys initiative indicate that the most common comorbidities include Post-Traumatic Stress Disorder (PTSD), Bipolar Disorder, and several anxiety disorders (such as Panic Disorder (PD) and General Anxiety Disorder (GAD)) (Wardenaar et al., 2018).

The most common treatments for MDD include antidepressant medication, psychotherapy/ cognitive behavioral therapy (CBT), or a combination of the two (National Institute of Mental Health, 2018). Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants, although other antidepressant medications that target different neurochemical pathways are available. Common alternative antidepressants include serotonin and norepinephrine reuptake inhibitors (SNRIs) and atypical antidepressants such as bupropion (Wellbutrin) (Kane, 2020; Moore and Mattison, 2017). Tricyclic antidepressants (TCAs) are less commonly prescribed, while monoamine oxidase inhibitors (MAOIs) are rarely prescribed due to side effects and drug interactions (Kane, 2020; Weyandt, 2019, p. 82). Additional psychopharmacological treatments may be added in order to augment the effects of commonly prescribed antidepressant medication, particularly in patients that do not respond to one or more courses of a singular antidepressant. Triiodothyronine (T3), lithium (Li), and atypical antipsychotics have all been shown to enhance the effects of antidepressants, although dosage should be carefully considered and patients should be monitored for potential adverse effects (Bauer et al., 2000; Dorée et al., 2007; Joffe, 2011; Morin, 2015; Nelson and Papakostas, 2009; Post, 2018; Thase, 2002; Touma et al., 2017; Wang and Si, 2013). Electroconvulsive therapy (ECT) can also be used in place of or as an augmentation to a course of antidepressant medication, with prior research suggesting that the greatest antidepressant effect can be achieved through a combination of the two treatments (Al-Harbi, 2012; Sackeim, 2017; Song et al., 2015).

Although antidepressant usage is highly prevalent in the U.S.—approximately 12.0% of adults reported filling one or more prescriptions for antidepressant medication (Moore and Mattison, 2017)—there are mixed reports on their efficacy. A 2010 meta-analysis found that antidepressant efficacy was dependent on symptom severity, and that for participants with mild to moderate symptoms, antidepressant medication was not significantly more beneficial than placebo (Fournier et al., 2010). A more recent meta-analysis of SSRI usage among U.S. adults aged 18 years or older found that while benefits of medication may be statistically significant compared to placebo, the clinical significance is more questionable, and SSRI usage is more likely to result in adverse effects (Jakobsen et al., 2017). Additionally, results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial showed that factors associated with lower remission rates after the first stage of treatment (level 1) with an SSRI include concurrent psychiatric disorders, especially anxiety or substance use disorders (Gaynes et al., 2009). A more recent study of treatment-resistant depression noted that co-occurring psychiatric conditions were a risk factor for lack of response to antidepressant treatment (Al-Harbi, 2012). A review of factors that influence prognosis and treatment outcome of depression also concluded that psychiatric comorbidities influence outcome regardless of whether patients receive treatment (Kraus et al., 2019).

.The U.S. Food and Drug Association (FDA) cleared the first commercial Transcranial Magnetic Stimulation (TMS) system in 2008; since then, many additional systems have been approved (McClintock et al., 2018). TMS is often used as an antidepressant treatment in treatment-resistant depression, or in a patient population that have not responded to or tolerated previous antidepressant medication trials (even if they have not been diagnosed with treatment-resistant depression) (Conelea et al., 2017; McClintock et al., 2018). TMS operates by passing a high-intensity current through a copper coil, producing a magnetic field that can be used to generate an electric field upon contact with the surface of the brain (Lefaucheur, 2019). This electric field is sufficient to produce action potentials and alter network activation within the cortex (Lefaucheur, 2019). It is not currently understood exactly how TMS exerts an antidepressant effect, but a systematic review by Noda et al. (2015) suggests that repetitive TMS (rTMS) exerts an antidepressant effect by altering neurochemical levels, blood flow, and other brain activity. Given the evidence questioning the efficacy of traditional antidepressant medications (such as SSRIs) and the likely relationship between comorbid diagnoses and decreased response to antidepressant regimes, the purpose of the present systematic review is to address the following questions: 1. Is TMS effective at treating MDD when it is comorbid with another psychiatric disorder? 2. Is TMS effective at simultaneously reducing the symptoms of the comorbid disorder?

Methods

Search and Retrieval

The systematic review of the literature was conducted in accordance with PRISMA guidelines (Liberati et al., 2009) between January – April 2020. Databases used for a comprehensive search included PubMed and Psyclnfo. The search query used to identify relevant articles was: ((major depression) AND (comorbid)) AND transcranial stimulation.

Eligibility Criteria

Studies were included in the review if they met the following criteria:

1. Were published between 2010-2020
2. Were originally published in English
3. Were not case studies (N > 1)
4. Were conducted using human participants (not animal models)
5. Therapeutic treatment was the intended purpose OR reduction in symptomology was the intended outcome (i.e. studies investigating predictors of responsiveness were excluded)

Studies were excluded from the review if:

1. Participants did not meet the criteria for diagnosed MDD
2. Participants did not meet the criteria for an additional diagnosed psychiatric disorder
3. The treatment intervention was not a form of transcranial magnetic stimulation (i.e. repetitive TMS (rTMS), synchronized TMS (sTMS), deep TMS (dTMS), etc.)

The search yielded 110 articles across both databases (PsycInfo = 38, PubMed = 72). After removing articles that did not meet the specified criteria, 15 articles remained eligible (PsycInfo = 7, PubMed = 8). Duplicate articles were not present within databases; after removing duplicate articles between databases, a total of 8 articles remained eligible for inclusion in the current review (Table 1).

Results

Demographic and Clinical Characteristics

Age of participants included in the present review ranged from 18 to 70 years old (Gwynette et al., 2020; Philip et al., 2019). Mean age was reported in 87.5% of studies; Gwynette et al. (2020) reported median age instead. From the available mean age data, a mean of mean ages was calculated (M = 47.51 years old). 87.5% of studies reported number or percentage of female participants; percentage of female participants ranged from 10-62.4% (M = 38.8%) (Carpenter et al., 2018; Clarke et al., 2019; Gwynette et al., 2020; Philip et al., 2019, 2016; White and Tavakoli, 2015). Reported mean age and percent of female participants from Clarke et al. (2019) were based solely on participants with comorbid anxiety. 25% of studies provided information on participants' reported race; a range of 90-94.3% of participants in these studies identified as Caucasian (Carpenter et al., 2018; Philip et al., 2016). Lastly, only 12.5% of studies provided any further demographic data: highest level of education and employment status (Carpenter et al., 2018).

Although not a requirement for inclusion into the current review, 75% of studies required participants to be non-responders to/intolerant of previous trials of antidepressant medication, or to be symptomatic despite a stable ongoing regime (Carpenter et al., 2018;

Clarke et al., 2019; Kumar et al., 2018; Mantovani et al., 2013; Philip et al., 2019, 2016). Where applicable, participants were allowed to continue stable treatment regimes, including antidepressant medication use and psychotherapy (Table 2) (Carpenter et al., 2018; Clarke et al., 2019; Gwynette et al., 2020; Mantovani et al., 2013; Philip et al., 2019, 2016).

In addition to diagnosed MDD, all studies contained participants with a diagnosed comorbid disorder. Clarke et al. (2019) included participants without a comorbid disorder as a control, while remaining participants met diagnostic criteria for one of several anxiety disorders (agoraphobia, generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), panic disorder (PD) with agoraphobia, post-traumatic stress disorder (PTSD), or social anxiety disorder (SAD)). Remaining studies investigated samples with the same comorbid diagnoses throughout. Comorbid disorders included in the review were agoraphobia, autism spectrum disorder (ASD), GAD, OCD, PD (with and without agoraphobia), PTSD, PD, and SAD (Table 3). PTSD and anxiety disorders were most represented among the comorbid diagnoses, which is consistent with their prevalence as comorbid disorders with MDD (Wardenaar et al., 2018).

Stimulation Parameters

All studies except for Philip et al. (2019) used repetitive TMS (rTMS) as a therapeutic intervention. Stimulation frequencies for rTMS ranged from 1 Hz (Clarke et al., 2019; Mantovani et al., 2013; White and Tavakoli, 2015) to 20 Hz (Kumar et al., 2018) (M = 8.2 Hz). 25% of studies (Clarke et al., 2019; Gwynette et al., 2020) utilized sequential bilateral stimulation in which a combination of high and low frequencies were used. All rTMS studies targeted a location within the prefrontal cortex (PFC). Carpenter et al. (2018) reported targeting the left PFC but further clarified the location as the dorsolateral PFC (dlPFC) using standard F3 location. The remaining studies specifically reported targeting the dorsolateral PFC (dlPFC) (typically located by measuring forward from motor cortex or using Beam F3 method; not all studies reported how dlPFC location was determined). 37.5% of studies (Gwynette et al., 2020; Kumar et al., 2018; Philip et al., 2016) stimulated only the left dlPFC, while 12.5% of studies (Mantovani et al., 2013) stimulated only the right dlPFC. White & Tavakoli (2015) bilaterally and sequentially stimulated the right and left dlPFC. Clarke et al. (2019) utilized either a unilateral stimulation to the right dlPFC or a bilateral sequential stimulation to the left and right dlPFC. Philip et al. (2019) utilized a different method of TMS (synchronized TMS or sTMS), which cannot be directly compared to rTMS (Table 4). However, outcome measures and conclusions are discussed for all studies. The general accordance of target locations among rTMS studies (in addition to the outcome measures, discussed later) confirmed that the PFC (and the dlPFC in particular) is an efficacious target for treatment of MDD, even with an additional comorbid disorder. Interestingly, rTMS treatment also appeared to be effective across a range of frequencies, contradicting prior findings that antidepressant effect may be frequency-dependent (Noda et al., 2015).

Treatment Duration

Number of treatment sessions (Table 4) was reported for 87.5% of studies and ranged from 20-40 sessions. 37.5% of studies (Carpenter et al., 2018; Gwynette et al., 2020; Kumar et al.,

2018) utilized a set number of treatment sessions and 50% of studies (Mantovani et al., 2013; Philip et al., 2019, 2016; White and Tavakoli, 2015) allowed participants some choice in treatment duration. Sham-controlled studies (Mantovani et al., 2013; Philip et al., 2019) in which participants were divided between treatment and sham conditions (phase 1) and allowed to continue active treatment (phase 2) found that the full 40-session treatment duration was more efficacious than the 20-session duration (greater reduction in depression symptomology). Using the greatest number of treatment sessions offered per study yields *M* = 33.9 treatment sessions, indicating that TMS requires time (up to a month or longer, depending on frequency of sessions) for a noticeable or significant antidepressant effect to occur (Table 5).

Outcome Measures

All studies used self-report or a combination of clinician-issued, self-report, and informant-report instrument as a measure of symptom severity at the starting point and endpoint of treatment (Tables 6 & 7). MDD measures varied across studies, which should be considered when generalizing results, as different measures have different score ranges for depression severity. However, antidepressant response criteria and remission criteria (where reported) were similar across studies, with response typically being designated as a reduction of ≥50% in depression measurement score from baseline, and remission measured as being < a designated depression measurement cut-off score.

Reduction in Symptomology

87.5% of studies reported results in terms of percentages of patients that meet response and remission criteria; 37.5% of studies also reported results using alternate measures, such as mean reduction in score(s) from baseline to end-of-study. Response and remission rates vary widely (Table 8); from the available data, a range of 39.5-70% of participants experienced an antidepressant response to treatment, and 16.6-76.9% of patients achieved remission from MDD. A range of 48.6-84.6% of participants responded to treatment of their comorbid disorder, and 50-84.6% achieved remission of comorbid symptoms.

Discussion & Limitations

All studies in this systematic review reported a significant reduction in depression symptomology from baseline to end-of-treatment, supporting the efficacy of TMS as a treatment for depression even when it presents with a comorbid condition (Carpenter et al., 2018; Clarke et al., 2019; Gwynette et al., 2020; Kumar et al., 2018; Mantovani et al., 2013; Philip et al., 2019, 2016; White and Tavakoli, 2015). Only Carpenter et al. (2018) reported serious adverse events in response to rTMS treatment; four participants (11.4%) experienced worsening symptoms with suicidality or suicidality with drug abuse. rTMS treatment was tolerated well by all other participants in this study and other studies included in the current review. No studies reported a mean increase in measure scores or MDD symptomology. Initial results show that TMS is an effective antidepressant across all included demographic variables (age, gender, and ethnicity), and response is not limited to a specific group. Lastly, results indicate that TMS may be an effective treatment for patients that have previously failed to respond to more conventional forms of treatment, such as medication or psychotherapy.

87.5% of studies reported a significant reduction in comorbid disorder symptomology from baseline to end-of-treatment (Carpenter et al., 2018; Clarke et al., 2019; Kumar et al., 2018; Mantovani et al., 2013; Philip et al., 2019, 2016; White and Tavakoli, 2015). In ASD, TMS appears to have a limited-to-null effect; Gwynette et al. (2020) reports no change in ASD symptomology over the course of treatment according to self-report data. Interestingly, informant reports indicate some improvement in symptomology, which the authors interpreted as indicating that rTMS may have some "possible effects" on core autism symptomology. Studies of PTSD reported a significant reduction in symptoms in response to active treatment (Carpenter et al., 2018; Clarke et al., 2019; Philip et al., 2019, 2016). Only Philip et al. (2019) included a sham condition for PTSD; although significant symptom reduction occurred in both conditions, the authors noted that the active treatment resulted in greater symptom reduction than the sham. Studies of PD (with or without agoraphobia) found a significant reduction in panic symptoms over the course of treatment (Clarke et al., 2019; Kumar et al., 2018; Mantovani et al., 2013). Mantovani et al. (2013) found a 50% response rate with active treatment compared to an 8% response rate with sham treatment. These results could indicate that PD responds more quickly to rTMS treatment than MDD, or that PD is selectively responsive to rTMS and not a placebo, but additional studies are necessary to support either of these conclusions. Studies of GAD found that rTMS treatment resulted in significant reduction of symptoms, although no sham comparison was included in these studies (Clarke et al., 2019; White and Tavakoli, 2015). Lastly, Clarke et al. (2019) reported on additional anxiety disorders such as agoraphobia, OCD, and SAD; rTMS treatment resulted in significant symptom reduction, although these results cannot be compared to a sham condition or additional studies.

Although TMS may be promising, there are several important limitations to consider. Due to the differences in how the location of the dlPFC was determined (or failure to report), it is difficult to confirm that all studies identified and treated the same area of the cortex. Additionally, study sizes vary from 10-248 participants, but 87.5% of studies utilized a sample size where $N < 50$ participants. If the large sample size of Clarke et al. (2019) is treated as an outlier and removed, the mean sample size $M = 19$ participants. Small sample size has been related to low statistical power, which can cause variability in the sample to appear greater and effect sizes to appear larger than they really are (Algermissen and Mehler, 2018). Statistical power was not reported in any study included in the present review. It is likely that these studies are underpowered due to limited sample sizes, making the findings less robust. Results should be interpreted cautiously, and further studies should be conducted for verification.

A serious limitation of the studies is that only 25% of studies (Mantovani et al., 2013; Philip et al., 2019) included a sham condition. A large placebo response has been observed in several MDD treatment methods, including TMS; sham-controlled studies may help to determine whether significant treatment effects can properly be attributed to TMS intervention (Brunoni et al., 2009; Duecker and Sack, 2015). Mantovani et al. (2013) found that there was no significant difference in antidepressant response or symptom reduction between the active-treatment and sham group at the end of phase 1 of the trial, although they acknowledge that this could be due to the 4-week time period and that it is possible that a difference would be seen if phase 1 had lasted for a longer duration. They did report a

significant reduction in symptoms in participants that received 8 weeks of active rTMS treatment. Philip et al. (2019) reported significant reductions in depression symptomology in both the active-treatment and sham conditions, although the active-treatment condition resulted in greater reduction of depression severity than the sham. Both studies indicated that participants were unable to distinguish between active and sham TMS.

As previously mentioned, many studies required participants to be non-responders to (or intolerant of) one or more courses of antidepressant medication, or to remain symptomatic despite stable treatment. Where applicable, participants were allowed to continue stable courses of treatment, including antidepressant medication or psychotherapy. Therefore, synergistic effects of TMS with additional treatments cannot be ruled out.

Lastly, participants in the included studies were primarily recruited from clinic populations or referred by a psychiatrist and may not be representative of the general population. Demographic information is lacking in most studies, and it is possible that ethnic and racial minorities are underrepresented (Carpenter et al., 2018; Philip et al., 2016). The participant population also skews male, with a mean 38.8% of participants identifying as female across studies that report gender. Additional demographic data is necessary to determine the extent to which results can be generalized.

Conclusion

Only 7.3% of articles in the initial search met inclusion and exclusion criteria for the current review, indicating a dearth of comorbidity studies in the available literature. Based on available data, TMS appears to significantly reduce symptoms of MDD and comorbid disorders, particularly PTSD and anxiety disorders. TMS treatment should be considered as an alternative option for patients who fail to respond to traditional treatments such as medication or psychotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The author would like to thank Dr. Lisa Weyandt at the Department of Psychology of the University of Rhode Island for providing guidance during the writing process and proofreading the initial draft. Research reported in this publication was supported by the National Center for Research Resources of the National Institute of Health under Award Number G20RR030883. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institute of Health.

Role of the Funding Source

The funding source had no involvement in gathering data, writing this review, or submission for publication.

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Highlights

- Major depression symptoms decrease in response to transcranial magnetic stimulation
- Comorbid symptomology decreases in response to transcranial magnetic stimulation

Table 1.

Articles included in current systematic review

Authors	Year of Publication	Title
Carpenter et al.	2018	5 Hz Repetitive transcranial magnetic stimulation for posttraumatic stress disorder comorbid with major depressive disorder
Clarke et al.	2019	Efficacy of repetitive transcranial magnetic stimulation in the treatment of depression with comorbid anxiety disorders
Gwynette et al.	2020	Treatment of Adults with Autism and Major Depressive Disorder Using Transcranial Magnetic Stimulation: An Open Label Pilot Study
Kumar et al.	2018	Effect of high-frequency repetitive transcranial magnetic stimulation (rTMS) in patients with comorbid panic disorder and major depression
Mantovani et al.	2013	Randomized sham controlled trial of repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex for the treatment of panic disorder with comorbid major depression
Philip et al.	2016	5-Hz Transcranial Magnetic Stimulation for Comorbid Posttraumatic Stress Disorder and Major Depression
Philip et al.	2019	Synchronized transcranial magnetic stimulation for posttraumatic stress disorder and comorbid major depression
White & Tavakoli	2015	Repetitive transcranial magnetic stimulation for treatment of major depressive disorder with comorbid generalized anxiety disorder

Table 2.

Individual study requirements for participant inclusion and treatment continuation

Author	Required Failure or Intolerance of Previous Pharmacologic Treatment	Number of Courses/ Medications	Concomitant Medication or Therapy Occurred
Carpenter	Yes	1+	Stable, ongoing psychotherapy permitted
Clarke	Yes	2+ (44.4% previously treated with ECT)	Treating psychiatrists requested not to make changes to patients' medication immediately before or during rTMS treatment
Gwynette	Yes	2+	Yes, medication regimes stable for 1+ months allowed
Kumar	Yes	2+	-
Mantovani	Yes, included if symptomatic despite treatment with an adequate medication trial	1+	Yes, stable medication regimes (1+ months) and therapy regimes (3+) months allowed
Philip (2016)			Yes; were in treatment at VA PTSD clinic "inclusive of medication and psychotherapy"
Philip (2019)	Yes, included "if applicable" if symptomatic despite stable treatment for at least 6 weeks		Yes, ongoing therapy allowed to continue
White	-	-	-

Table 3.

Comorbid disorders included in sample and relative representation. Note that number of studies featured is greater than the number of studies included in the review because one study investigates multiple comorbid anxiety disorders

Psychological Disorder	Number of Studies Featured In
Agoraphobia	1
ASD	1
GAD	2
OCD	1
PD (with or without agoraphobia)	3
PTSD	4
SAD	1

Table 4.

rTMS studies and parameters

Authors	Stimulation Frequency (or Order of Stimulation)	Unilateral or Bilateral Stimulation	Side (or Order of Stimulation)	Cortical Location
Carpenter et al.	5 Hz	Unilateral	Left	PFC
Clarke et al.	1 Hz	Unilateral	Right	dlPFC
	10 Hz – 1 Hz	Bilateral	Left – Right	
Gwynette et al.	10 Hz	Unilateral	Left	dlPFC
Kumar et al.	20 Hz	Unilateral	Left	dlPFC
Mantovani et al.	1 Hz	Unilateral	Right	dlPFC
Philip et al. (2016)	5 Hz	Unilateral	Left	dlPFC
White & Tavakoli	1 Hz – 10 Hz	Bilateral	Right – Left	dlPFC

Table 5.

Treatment duration by study; dashes indicate that data were unreported

Authors	Number of Treatment Sessions	Length of Treatment (in Weeks)
Carpenter et al.	40	10
Clarke et al.	-	-
Gwynette et al.	25	-
Kumar et al.	20	4
Mantovani et al.	20-40	4-8
Philip et al. (2016)	Up to 36	-
Philip et al.	20-40	4-8
White & Tavakoli	24-36	5-6

Table 6.

Depression instruments utilized by study; dashes indicate that criteria or data were unreported

Authors	Depression Instrument(s) Utilized	Response Criteria	Remission Criteria
Carpenter et al.	Inventory of Depression Symptomology-Self Report (IDS-SR)	≥ 50% reduction from baseline IDS-SR score	IDS-SR score ≤ 14 post-treatment
Clarke et al.	21-Item Hamilton Depression Rating Scale (HDRS21) Montgomery-Asberg Depression Rating Scale (MADRS) Zung Self-Rating Depression Scale (ZUNG)	Improvement ≥ 50% from baseline of HDRS21	Final HDRS21 score ≤ 7
Gwynette et al.	HDRS17	-	-
Kumar et al.	HDRS	≥ 50% reduction from baseline HDRS score	-
Mantovani et al.	HDRS24 ZUNG Beck Depression Inventory- II (BDI-II)	≥ 50% reduction from baseline HDRS24 score	Final HDRS score < 10
Philip et al. (2016)	Quick Inventory of Depression Symptomology (QIDS)	“Reliable change” > 5- point symptom score change in QIDS	
Philip et al. (2019)	QIDS	-	-
White & Tavakoli	HDRS21 QIDS	≥ 50% reduction in symptoms from baseline	HDRS21 score < 8

Table 7.

Additional outcome measures utilized by study; dashes indicate that criteria or data were unreported

Authors	Additional Outcome Measure(s) Utilized	Comorbid Disorder Response Criteria	Comorbid Disorder Remission Criteria
Carpenter et al.	PTSD Checklist for DSM-5 (PCL-5) Clinician measure of Global Illness Severity (CGI-S) Patient measure of Global Illness Severity (PGI-S) Clinician measure of Global Illness Improvement (CGI-I) Patient Measure of Global Illness Improvement (PGI-I) Patient Health Questionnaire (PHQ-9) Depression Anxiety Stress Scale (DASS) Perceived Stress Scale (PSS)	"Clinically meaningful improvement" ≥10 point reduction from baseline PCL-5 score "Categorical response" when post-treatment score on PCL-5 ≤ 33 combined with clinically meaningful improvement	-
Clarke et al.	Hamilton Anxiety Rating Scale (HAM-A)	-	-
Gwynette et al.	Social Responsiveness Scale, 2nd Edition (SRS-2) Ritvo Autism Aspergers Diagnostic Scale-Revised (RAADS-R) Aberrant Behavior Checklist (ABC) Repetitive Behavior Scale-Revised (RBS-R)	-	-
Kumar et al.	Panic Disorder Severity Scale (PDSS)	Reduction ≥ 40% from baseline PDSS score	-
Mantovani et al.	PDSS Panic Disorder Severity Scale-Self Report (PDSS-SR) HAM-A CGI-S Social Adaptation Self-evaluation Scale (SASS)	Reduction ≥ 40% from baseline PDSS score	Final PDSS score < 5
Philip et al. (2016)	PCL	"Reliable change"> 10-point symptom score change in PCL	-
Philip et al. (2019)	PCL	-	-
White & Tavakoli	General Anxiety Disorder-7 (GAD-7) PHQ-9	≥ 50% reduction in symptoms from baseline	GAD-7 score < 5

Table 8.

Percentage of participants that met response and remission criteria by study; dashes indicate that results were unreported

Authors	Percentage of Participants that Met Antidepressant Response Criteria	Percentage of Participants that Met MDD Remission Criteria	Percentage of Participants that Response Criteria for Comorbid Disorder	Percentage of Participants that Met Remission Criteria for Comorbid Disorder
Carpenter et al.	42.9%	34.3%	48.6%	-
Clarke et al.	39.5%	23.3%	-	-
Gwynette et al.	70%	40%	-	-
Kumar et al.	46.2%	-	53.8%	-
Mantovani et al.	50% of patients assigned to active treatment	16.6% of patients assigned to active treatment	67% of patients assigned to active treatment	50% of patients assigned to active treatment
Philip et al. (2016)	50%	20%	40%	-
Philip et al. (2019)	-	-	-	-
White & Tavakoli	69.2%	76.9%	84.6%	84.6%